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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,586	06/19/2001	Yann Echelard	10275-120001 / GTC-31 US	2580

31904 7590 10/21/2003

GTC BIOTHERAPEUTICS, INC.
175 CROSSING BOULEVARD, SUITE 410
FRAMINGHAM, MA 01702

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	19

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,586	ECHELARD ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *10,13 and 16-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,12,14,15 and 32-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed on 7/14/03 in Paper No. 18 has been entered.

Claims 1-40 are pending in the present application.

This application contains claims 10, 13 and 16-31 drawn to an invention nonelected with traverse in Paper No. 14. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Amended claims 1-9, 11-12, 14-15 and new claims 32-40 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-15 and 37-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **The following are new grounds of rejection that were necessitated by applicants' amendment of the claims in Paper No. 18.**

Claims 9 and 12 recites the limitation "the cell" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim. This is because in their respective independent claims 8 and 11, there is no recitation of a cell, but only a

fertilized egg. Therefore, the metes and bounds of the claims are not clearly determined.

Similarly, claims 14 and 15 recite the limitation "the cell" in the third paragraph and line 1 of the claims, respectively. There is insufficient antecedent basis for this limitation in the claim. Therefore, the metes and bounds of the claims are not clearly detemined.

In claim 11, the phrase "allowing said fertilized egg to give rise to a transgenic non-human mammal" is unclear. Which fertilized egg? The fertilized egg with the first nucleic acid sequence or the fertilized egg with a second nucleic acid sequence or the fertilized egg with both the first and second nucleic acid sequences? The metes and bounds of the claims are not clearly determined.

In claims 37 and 38, it is unclear what is encompassed by the phrases "said first and said second sequences are inserted together", "said first and said second sequences are inserted separately", respectively. How can the first sequence being inserted together with the second sequence when the second sequence is introduced into a fertilized egg from a transgenic non-human mammal whose germ and somatic cells already comprise the first sequence? Or do Applicants mean the first and second sequences being inserted at the same or separate sites in the genome of a transgenic non-human mammal? The metes and bounds of the claims are not clearly determined.

Similarly, it is unclear what is encompassed by the phrases "said first and said second sequences are inserted together", "said first and said second sequences are inserted separately" in claims 39 and 40, respectively. How can the first sequence

being inserted together with the second sequence when the second sequence is clearly introduced into a fertilized egg after the first sequence as recited in claim 11? Or do Applicants mean the first and second sequences being inserted at the same or separate sites in the genome of a transgenic non-human mammal? The metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1-8, 11, 14, 32-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houdebine et al. (U.S. Patent No. 5,965,788) in view of Eichner et al. (U.S. Patent No. 5,665,567; IDS), Yansue et al. (U.S. Patent No. 5,834,269) and Hart et

al. (Science 240:1529-1521, 1988; IDS). **This is a new gr und of rejection necessitated by Applicants' amendment.**

Houbedine et al. teach a method of producing a transgenic non-human mammal whose genome comprises a DNA construct comprising a rabbit WAP promoter directing the expression of a DNA sequence encoding a heterologous protein. Houbedine et al. also teach methods of using the transgenic non-human mammal in the production of recoverable amounts of a heterologous protein in the mammal's milk, and that the mammal is a bioreactor for a protein of interest (see abstract and the claims). Houdebine et al. listed different heterologous proteins to be expressed such as growth factors, interleukins, stimulating factors, kinases, coagulation factors among others (see col. 4), and various promoters (e.g., alpha-casein, beta-casein, beta-lactoglobulin, WAP) that have been used to make transgenic non-human mammals expressing heterologous protein in their milk (see Table 1). Houdebine et al. also teach that the DNA constructs are introduced by microinjection into fertilized eggs at the one cell up to the 8-cell stage in the making of the transgenic non-human mammals (see col. 2, lines 57-61).

Houdebine et al. do not specifically teach a method of producing a transgenic non-human mammal capable of expressing an active PDGF molecule in its milk or a method of producing a glycosylated PDGF using the same or the same methods utilizing a nucleic acid construct containing an insulator sequence inserted on either side of a nucleic acid sequence encoding PDGF.

However, at the effective filing date of the present application, Eichner et al. teach that cDNA clones encoding for the PDGF-A chain and PDGF-B chains are available and that different routes for preparing recombinant PDGF homodimers are known (see col. 3, lines 32-53; col. 4, lines 34-38). Additionally, recombinant PDGF-AB heterodimers have been prepared in eukaryotic expression systems wherein both PDGF-A and PDGF-B genes are located on one vector in independent transcription units (col. 4, lines 48-59). Eichner et al. further teach that it is known in the literature that when both PDGF genes are expressed in a eukaryotic cell, 30% or more of the produced PDGF is in the form of a homodimer (col. 5, lines 5-9). Moreover, Eichner et al. disclose the use of a biscistronic expression vector system in which an IRES sequence is located between the first and second cistrons and in which the PDGF-B chain coding gene is located in the first cistron to produce predominantly recombinant PDGF-AB heterodimers (see abstract and the claims). The PDGF-species are involved in the wound healing process, and the most frequent isoform PDGF-AB has been taught by Eichner et al. to be formulated in a pharmaceutical preparation for wound healing, for skin regeneration, skin smoothening, for preventing of scaring or of skin ageing or for sunburn (see col. 3, line 64 continues to line 2 of col. 4; col. 7, lines 46-62).

Yasue et al. also teach that an exogenous gene that is introduced into a fertilized egg should be placed between insulators so as to ensure an insulated environment, such that the introduced exogenous gene will not be affected by any influence from adjacent genes in the fertilized egg and thus allowing correct expression of introduced

exogenous gene to produce desired transgenic organism (see Summary of the Invention).

Hart et al. also teach that there are two populations of PDGF receptor that differ in ligand-binding specificity for the PDGF species. It is reported that the B receptor binds only the PDGF-BB dimmers whereas the A/B receptor binds PDGF-AA, PDGF-BB and PDGF-AB dimmers and that human dermal fibroblasts appear to express seven times as much as B receptor as A/B receptor (see abstract). Other cell types have been noted to have different ratio for the two classes of PDGF receptor (page 1531, col. 1, bottom of the first full paragraph).

Accordingly, it would have been obvious and within the scope of a skilled artisan to modify the methods taught by Houdebine et al. by introducing a nucleic acid sequence encoding a PDGF-A chain and/or a PDGF-B chain either in separate nucleic acid molecules or in a biscistronic expression vector into a fertilized egg, wherein the nucleic acid sequence is operatively linked to a promoter which directs the expression of a PDGF mammary gland epithelial cells, and wherein the nucleic acid sequence is flanked by insulator sequences in light of the teachings of Eichner et al. and Yasue et al. to produce a non-human transgenic mammal capable of expressing an active PDGF molecule in its milk, and for preparing transgenically produced PDGF using the same for the reasons discussed below.

One of ordinary skilled artisan would have been motivated to carry out the above modification because the mitogenic PDGF-species are involved in the wound healing process, and the most frequent isoform PDGF-AB has been taught by Eichner et al. to

be formulated in a pharmaceutical preparation for wound healing, for skin regeneration, skin smoothening, for preventing of scaring or of skin ageing or for sunburn (see col. 3, line 64 continues to line 2 of col. 4; col. 7, lines 46-62). Therefore, there was a need in the prior art at the effective filing date of the present application for obtaining a significant quantity of purified and biologically active PDGF-species for the preparation of pharmaceutical compositions. Furthermore, Houdebine et al. already teach that the production of a recombinant protein secreted in the milk of a non-human transgenic mammal provides a highly desirable system for obtaining the recombinant protein in large quantities, in mature state due to proper glycosylation, phosphorylation and enzymatic processing, as well as the relative ease of collecting and recovering the recombinant protein in milk (see col. 1, lines 30-41). Additionally, as taught by Yasue et al., the utilization of insulator sequences flanking the nucleic acid sequence encoding PDGF would eliminate any influence from adjacent genes in a genome of the transgenic non-human mammal and thus allowing correct expression of active PDGF in mammary glands to produce the recombinant PDGF in milk.

With respect to claim 14, it would also have been obvious and within the scope of skill for an ordinary skilled artisan to introduce into a fertilized egg obtained from a non-human transgenic mammal whose germ cell and somatic cells already containing a nucleic acid sequence encoding a PDGF-A chain operably linked to a promoter which directs expression in mammary epithelial cells with a nucleic acid sequence encoding a PDGF-B chain operably linked to a promoter which directs expression in mammary epithelial cells in light of the teachings of Hart et al. One of ordinary skilled artisan

would have been motivated to carry out the above modification to obtain different ratios of PDGF species in the transgenically produced milk that would produce different effects on different treated cell types depending on their differentially expressed B and A/B receptors. This is because Hart et al. already teach that the B receptor binds only the PDGF-BB dimmers whereas the A/B receptor binds PDGF-AA, PDGF-BB and PDGF-AB dimmers and that human dermal fibroblasts and other cell types appear to express different ratios of the two classes B receptor as A/B receptor (see abstract).

Given the teachings provided by Houdebine et al., Eichner et al., Yasue et al., Hart et al., and a high level of skills of an ordinary skilled artisan at the effective filing date of the present application, one of ordinary skilled artisan would have a reasonable expectation of success to practice the presently claimed invention.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Amendment

Applicants' arguments related to the above rejection in the Amendment filed on 7/14/03 in Paper No. 18 (pages 9-13) have been fully considered, but they are not found to be persuasive.

Applicants argue mainly that the Eichner et al. reference is a non-analogous art that does not make up for the deficiencies of the Houdebine et al. reference because Eichner et al. reference fails to provide any discussion of any expression system other than *in vitro* cell culture conditions and therefore it fails to understand or make obvious

the true nature of the present invention. The Hart et al. reference also fails to provide what the Houdebine and Eichner references lack. Applicants further argue that the combination of the cited references is a result of an improper hindsight, and that the prior art fails to provide the suggestion, or incentive to combine as well as a reasonable expectation of success.

In response to applicant's argument that the Eichner et al. is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Eichner et al. teach clearly that cDNA clones encoding for the PDGF-A chain and PDGF-B chains are available and that different routes for preparing active recombinant active PDGF homodimers as well as PDGF heterodimers for preparation of pharmaceutical compositions containing PDGF species. Although Eichner et al. do not explicitly discuss any expression system other than the *in vitro* cell culture expression systems, there was a clear need in the prior art at the effective filing date of the present application for obtaining a significant quantity of purified and biologically active PDGF-species for the preparation of pharmaceutical compositions. Also at the effective filing date of the present application, Houdebine et al. teach clearly that the production of a recombinant protein, including any growth factors, secreted in the milk of a non-human transgenic mammal provides a highly desirable system for obtaining the recombinant protein in large quantities, in mature state due to proper

glycosylation, phosphorylation and enzymatic processing, as well as the relative ease of collecting and recovering the recombinant protein in milk (see col. 1, lines 30-41). Therefore, the Eichner et al. reference is reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. The Hart reference provides teachings that different PDGF species elicit different biological responses on the different cell types depending on the availability of different types of PDGF receptors on the cell types.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Eichner et al. teach advantages and needs for the production of PDGF-AA, PDGF-BB, PDGF-AB. Houdebine et al. teach clearly that a non-human transgenic mammal provides a highly desirable system for obtaining a recombinant protein in large quantities (e.g., growth factors), in mature state due to proper glycosylation, phosphorylation and enzymatic processing, as well as the relative ease of collecting and recovering the recombinant protein in its milk (see col. 1, lines 30-41).

In response to Applicant's argument that the combination of the cited teachings has no reasonable expectation of success, Examiner notes that Houdebine et al. have

successfully produce numerous heterologous proteins (e.g., erythropoietin, G-CSF, α1-antitrypsin, urokinase, hirudin, factor VIII, any growth factor, any interleukin, any kinases, as well as any coagulation factors) in any non-human mammal's milk. Applicants have not provided any scientific reasons why an ordinary skilled artisan would not have a reasonable expectation of success for expressing biological active PDGF in milk of a transgenic non-human mammal, given high level of skills of an ordinary skilled artisan at the effective filing date of the present application for producing a heterologous protein in milk of a transgenic non-human mammal.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Zeta Adams, whose telephone number is (703) 305-3291.

Quang Nguyen, Ph.D.

Gerald A. Leffers Jr.

GERRY LEFFERS
PRIMARY EXAMINER